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The gut-heart connection: how the microbiome influences cardiovascular health

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Abstract

The gut-heart connection has emerged as a significant area of research, revealing how gut microbiota influences cardiovascular disease (CVD) pathophysiology. The gut microbiota has a significant impact on cardiovascular health through its involvement in endothelial function, systemic inflammation, cholesterol metabolism, and metabolic balance. Atherosclerosis, hypertension, myocardial infarction, and heart failure have all been linked to dysbiosis, an imbalance in the makeup of microorganisms. Important metabolites produced by microorganisms have a direct effect on vascular integrity, thrombosis risk, and lipid metabolism. These include trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), and secondary bile acids. There is potential for lowering the risk of CVD by addressing the gut microbiota through dietary changes, probiotics, prebiotics, and customized microbiome-based therapies. Implementing microbiome-based cardiovascular therapy is still hampered by differences in gut microbiota makeup, difficulties with clinical translation, and the requirement for standardized procedures. This review examines existing treatment approaches, future directions in microbiome research, and the processes underpinning the gut microbiome's influence on CVD. Establishing microbiome-targeted therapies in clinical cardiology requires extensive, long-term research incorporating multi-omics techniques.

Keywords: Gut microbiome; Cardiovascular disease; Dysbiosis; Trimethylamine N-oxide; Microbiome-based therapy

1. Introduction

Globally, cardiovascular diseases (CVDs) continue to be the primary cause of morbidity and mortality, and there is mounting evidence that the gut microbiota plays a part in cardiovascular health [1]. The gut-heart link is the term used to describe the reciprocal relationship between gut microbiota and circulatory function, which is mainly mediated by immune modulation, systemic inflammation, and microbial metabolites [2]. Bacteria, viruses, and fungi are among the trillions of microorganisms that live in the human gut and are essential for preserving immunological and metabolic equilibrium [3]. Atrial fibrillation, heart failure, atherosclerosis, and hypertension are among the cardiovascular disorders that have been connected to dysbiosis, or changes in the microbial makeup [4].

According to recent research, gut-derived metabolites such imidazole propionate, short-chain fatty acids, and trimethylamine N-oxide (TMAO) have a major impact on cardiovascular risk factors [4,5]. Bacterial endotoxins, like lipopolysaccharides (LPS), can enter the bloodstream through increased gut permeability brought on by dysbiosis, which accelerates cardiovascular damage and causes systemic inflammation [6].

Growing interest in gut microbiome-targeting therapeutic approaches, such as dietary changes, probiotics, prebiotics, and tailored microbiome-based therapeutics, has resulted from this new findings [2].

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2. The Role of the Gut Microbiome in Cardiovascular Health

The regulation of metabolic, immunological, and inflammatory processes that affect cardiovascular health is largely dependent on the gut microbiota [2]. While an imbalance dysbiosis has been connected to a higher risk of atherosclerosis, myocardial infarction, and heart failure, a balanced gut microbiota aids in blood pressure regulation, cholesterol metabolism, and vascular homeostasis [7,4]. The production of important microbial metabolites is changed by dysbiosis, which results in metabolic abnormalities, endothelial dysfunction, and systemic inflammation all of which are linked to the emergence of cardiovascular illnesses [1].

Trimethylamine N-oxide (TMAO), which is produced by gut microbial metabolism from dietary choline, L-carnitine, and betaine, is one of the most researched microbial metabolites in cardiovascular disease [3]. Platelet hyperactivity, the development of atherosclerotic plaque, and an increased risk of serious adverse cardiovascular events have all been closely linked to elevated levels of TMAO [5]. Furthermore, a microbial signature of dysbiosis, a high Firmicutes-to-Bacteroidetes ratio, has been linked to metabolic syndrome and hypertension, underscoring the connection between microbial composition and cardiovascular risk [6].

Short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, have also been discovered by recent studies to be protective metabolites generated by gut bacteria [2]. Through immune response modulation, gut barrier integrity enhancement, and blood pressure regulation through interactions with the renin-angiotensin system, SCFAs have anti-inflammatory and antihypertensive effects [1]. Furthermore, a recent study showed that imidazole propionate, another metabolite generated from the gut, influences metabolic and inflammatory pathways and is associated with the severity of heart failure [4].

These results highlight how crucial it is to preserve the balance of the gut microbiota for cardiovascular health. Gaining insight into the metabolic and molecular relationships between gut microorganisms and the cardiovascular system opens up new avenues for microbiota-focused therapeutic approaches.

3. Mechanisms Linking the Gut Microbiome to Cardiovascular Disease

The generation of microbial metabolites, immunological regulation, gut barrier integrity, and systemic inflammation are just a few of the ways that the gut microbiota affects cardiovascular health [2, 4]. Chronic low-grade inflammation can be brought on by microbial toxins such lipopolysaccharides (LPS) entering the bloodstream due to increased gut permeability caused by dysbiosis, which is defined as an imbalance between beneficial and detrimental gut bacteria [6]. Hypertension, myocardial dysfunction, and atherosclerosis are all influenced by this inflammatory cascade [3].

Trimethylamine N-oxide (TMAO), a major microbial-derived metabolite that impacts cardiovascular health, is created when gut bacteria break down dietary choline, L-carnitine, and phosphatidylcholine [1]. Higher incidences of myocardial infarction and stroke, endothelial dysfunction, and enhanced platelet aggregation have all been linked to elevated plasma TMAO levels [5]. Higher levels of TMAO were associated with worse clinical outcomes and more severe cardiac dysfunction in a study that looked at the composition of the gut microbiota in heart failure patients [4].

Furthermore, gut bacteria that digest dietary fiber produce short-chain fatty acids (SCFAs) such butyrate, acetate, and propionate, which are protective for cardiovascular health. By modifying immune cells and neurotransmitter signalling, SCFAs aid in blood pressure regulation, inflammation reduction, and endothelial function enhancement. Patients with heart failure, metabolic syndrome, and hypertension have been found to have low levels of SCFAs, which may indicate a possible therapeutic role for therapies that target the microbiota [2,7,8].

Imidazole propionate (ImP), a metabolite generated from the gut that increases oxidative stress and systemic inflammation, has also been discovered in recent studies to exacerbate the severity of heart failure. Further supporting the gut-heart relationship is phenylacetylglutamine (PAG), another microbial metabolite that has been connected to elevated platelet activation and a higher risk of thrombosis [2,4].

The gut-liver-heart axis is also important for the development of cardiovascular disease. Increased low-density lipoprotein (LDL) cholesterol and an increased risk of cardiovascular disease are the results of bile acid metabolism changes brought on by dysbiosis, which also affects lipid homeostasis. Uremic toxins are more prevalent in patients with chronic kidney illness, who frequently have imbalances in their gut flora. These uremic toxins can lead to heart failure and vascular calcification [5,6,9]. All things considered, our results show how intricately gut microbiota,

microbial metabolites, and cardiovascular health interact, underscoring the necessity of treatment approaches that focus on gut microbiome modulation.

4. Systemic Inflammation and Endothelial Dysfunction in Cardiovascular Disease

In the gut-heart axis, systemic inflammation is crucial because gut dysbiosis can trigger long-term inflammatory reactions that lead to endothelial dysfunction, hypertension, and atherosclerosis. Microbial imbalances cause increased gut permeability, which lets bacterial endotoxins like lipopolysaccharides (LPS) into the bloodstream and trigger vascular inflammation and immunological activation. Higher levels of circulating LPS have been related in studies to an elevated risk of cardiovascular disease (CVD), especially in circumstances like myocardial infarction and heart failure [3,8,10].

According to a recent study, certain strains of Firmicutes and Parabacteroides merdae are linked to higher levels of serum C-reactive protein (CRP), a crucial inflammatory marker connected to cardiovascular risk. Additionally, pro-inflammatory cytokines including IL-6, TNF-α, and IL-1β are activated by inflammation caused by dysbiosis, which leads to arterial stiffness and vascular endothelial dysfunction. These cytokines have been linked to the development of atrial fibrillation and hypertension, highlighting the part inflammation plays in cardiovascular disease [6,7,11].

Newer studies additionally emphasize how microbial metabolites such imidazole propionate (ImP) and TMAO contribute to endothelial dysfunction. It was discovered that elevated ImP levels were associated with deteriorating heart failure severity and compromised vascular function, indicating that gut-derived metabolites are important in regulating vascular inflammation. Further connecting microbial imbalances to hypertension and cardiovascular dysfunction is the evidence that gut dysbiosis impacts the renin-angiotensin-aldosterone system (RAAS), a vital blood pressure regulator [1, 2, 4].

5. Gut Microbiota and Cholesterol Metabolism in Cardiovascular Disease

An important factor in cardiovascular health is cholesterol metabolism, and there is mounting evidence that the gut microbiota has a major impact on lipid homeostasis and the development of atherosclerosis. It has been determined that some gut bacteria, such as those belonging to the genera Oscillibacter and Eubacterium, are important modulators of cholesterol metabolism, which lowers plasma cholesterol levels and improves lipid profiles. By producing enzymes that break down cholesterol and bile acids, these bacteria reduce the absorption of cholesterol in the intestines and the buildup of lipids throughout the body [12,13,14].

Conversely, dysbiosis is associated with elevated levels of triglycerides and low-density lipoprotein (LDL) cholesterol, both of which play a significant role in the development of atherosclerotic plaque. According to studies, abnormalities in gut microbiota result in changed bile acid metabolism, which hinders the removal of cholesterol and promotes the buildup of pro-atherogenic lipids. Furthermore, hepatic lipid dysregulation and chronic inflammation have been linked to gut-derived lipopolysaccharides (LPS), which exacerbate the course of cardiovascular disease [12,13,14].

Furthermore, gut microbes affect the function of high-density lipoproteins (HDL), which are protective for cardiovascular health. The removal of excess cholesterol from peripheral tissues and the prevention of atherosclerosis depends on HDL-mediated reverse cholesterol transport, which is enhanced by certain microbial species. On the other hand, gut microbiota dysbiosis compositions have been linked to malfunctioning HDL particles, which raises the risk of cardiovascular disease and impairs cholesterol efflux [12,13,14]. Probiotic and prebiotic supplements are among the recent therapies that target the gut microbiota and have demonstrated promise in lowering atherogenic lipid profiles and modifying cholesterol metabolism [12].

6. Gut Microbiome-Derived Metabolites and Their Impact on Cardiovascular Disease

Cardiovascular health is greatly impacted by the range of bioactive metabolites produced by the gut microbiota. Atherosclerosis, heart failure, and hypertension have all been well investigated in relation to trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), phenylacetylglutamine (PAG), and secondary bile acids [15,16].

6.1. Trimethylamine N-Oxide (TMAO) and Cardiovascular Risk

Dietary choline, L-carnitine, and phosphatidylcholine found in red meat, eggs, and dairy products are broken down by gut bacteria to create TMAO. Flavin-containing monooxygenases (FMOs) in the liver transform trimethylamine (TMA) into TMAO after it has been absorbed. Increased platelet aggregation, endothelial dysfunction, and a higher risk of

serious cardiovascular events, such as myocardial infarction and stroke, have all been connected to elevated plasma TMAO levels. According to research, TMAO increases the formation of arterial plaque by disrupting reverse cholesterol transport, which in turn causes atherosclerosis [9,10,16].

6.2. Short-Chain Fatty Acids (SCFAs) and Cardiovascular Protection

The microbial fermentation products of dietary fiber, SCFAs butyrate, acetate, and propionate, have been demonstrated to have beneficial cardiovascular effects in contrast to TMAO. By regulating vasodilation and endothelial function and interacting with the renin-angiotensin system (RAAS), SCFAs lower blood pressure. Studies have shown that low SCFA levels are associated with increased inflammation and endothelial dysfunction, both of which contribute to hypertension and cardiovascular disease progression [9,15,16].

6.3. Phenylacetylglutamine (PAG) and Thrombosis

PAG is another gut-derived metabolite linked to elevated platelet activation and thrombosis risk, according to recent studies. It has been demonstrated that PAG, which is produced when gut bacteria break down dietary phenylalanine**,** increases the risk of cardiovascular events by encouraging the formation of clots [9, 10].

6.4. Secondary Bile Acids and Lipid Metabolism

Bile acid metabolism, which has a direct impact on cholesterol levels and lipid homeostasis, is another important function of the gut microbiota. The signalling effects of primary bile acids on hepatic cholesterol synthesis and absorption are changed by some gut bacteria, which change them into secondary bile acids. Atherosclerosis and hypercholesterolemia have been associated with bile acid abnormalities brought on by dysbiosis [9,10,15].

7. Dietary Modifications and Microbiome-Targeted Interventions for Cardiovascular Disease

One promising strategy for lowering the risk of cardiovascular disease (CVD) is altering the gut microbiome through dietary changes and microbiome-targeted treatments. According to research, dietary patterns have a major impact on systemic inflammation, metabolite synthesis, and gut bacteria composition all of which have an effect on cardiovascular health [12,14].

7.1. The Role of Diet in Modulating the Gut Microbiome

It has been demonstrated that diets high in fiber, polyphenols, and polyunsaturated fatty acids (PUFAs) support a more wholesome gut flora, which lowers inflammation and improves lipid metabolism. For instance, the Mediterranean diet, which prioritizes fruits, vegetables, whole grains, olive oil, and lean protein, has been linked to higher production of short-chain fatty acids (SCFAs), which are important for controlling endothelial function and blood pressure. On the other hand, a Western diet that is heavy in processed foods, saturated fats, and refined sugars raises the risk of cardiovascular disease, induces gut dysbiosis, and increases the formation of trimethylamine N-oxide (TMAO) [12,13,17].

7.2. Probiotics and Prebiotics in Cardiovascular Health

The ability to restore gut microbiota balance and lower the risk of CVD has been investigated for probiotics, which are living microorganisms that offer health benefits, and prebiotics, which are non-digestible fibers that support good gut flora. Certain probiotic species, like Bifidobacterium and Lactobacillus, have been shown to improve endothelial function, lower cholesterol, and decrease inflammatory markers. Increased synthesis of SCFA and positive changes in gut microbiota have been linked to prebiotic supplementation, especially with inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS) [13,14,17].

7.3. Microbiome-Based Therapeutics

Precision probiotics, microbial enzyme inhibition therapy, and fecal microbiota transplantation (FMT) are examples of emerging microbiome-targeted therapies that show potential in modifying cardiovascular risk factors. FMT has been investigated for its ability to restore gut microbial diversity and lower inflammation-associated cardiovascular risk. It entails transferring fecal microbiota from a healthy donor to a recipient. Furthermore, one tactic to lessen TMAO's pro-atherogenic effects would be to suppress the microbial enzymes that produce it [12,14,17].

8. Personalized Microbiome-Based Approaches for Cardiovascular Disease Management

Personalized microbiome-based therapeutics are becoming a viable approach to customizing the treatment of cardiovascular disease (CVD) as research on the gut-heart axis progresses. Precision medicine techniques seek to tailor microbiome-targeted therapies according to each person's distinct microbial profile, taking into account the inter-individual heterogeneity in gut microbiota composition [13,17].

8.1. Microbiome Profiling for Risk Assessment

The identification of unique microbial signatures linked to cardiovascular disorders has been made possible by microbiome study employing metagenomics and next-generation sequencing (NGS). Patients who have insufficient synthesis of short-chain fatty acids (SCFA) or high levels of trimethylamine N-oxide (TMAO) may be more susceptible to heart failure, hypertension, and atherosclerosis. Clinicians can anticipate illness risk and tailor pharmacological or nutritional therapies based on advanced microbiome profiling [12,13,14].

8.2. Tailoring Probiotics and Prebiotics to Individual Microbiomes

In contrast to the one-size-fits-all strategy, customized medicine aims to match the composition of a person's gut microbiota with particular probiotic and prebiotic compositions. Some strains of Lactobacillus and Bifidobacterium may help individuals with inflammation caused by gut dysbiosis, while others may be better at regulating cholesterol metabolism and lowering blood pressure. Based on a patient's microbiome profile, computational models are being created to forecast which probiotic strains will be best for them [13,14,17].

8.3. Microbial-Derived Therapeutics

In addition to probiotics, scientists are looking into treatments based on microbial metabolites that target particular cardiovascular risk factors. For instance, controlling bile acid metabolism with certain gut microbiota therapies may lower the risk of atherosclerosis by regulating cholesterol and lipid balance. Similarly, a unique approach to lower the cardiovascular risk associated with TMAO is the suppression of microbial TMA synthesis enzymes, such as cutC and cutD [12,14,17].

8.4. Challenges and Future Directions

Although personalized microbiome-based therapies hold great potential, there are still obstacles in implementing these discoveries in clinical settings. Implementing microbiome-targeted therapeutics is made more difficult by variations in research populations, dietary practices, and the limits of standardized microbiome analysis methodologies. Establishing clinical objectives, improving microbiome-based diagnostics, and creating focused therapies suited to various genetic and cultural backgrounds will require more study [13,17].

9. Challenges and Future Directions in Gut Microbiome and Cardiovascular Disease Research

Although the gut-heart axis provides encouraging information for managing and preventing cardiovascular disease (CVD), there are still a number of obstacles to overcome before microbiome research can be applied in therapeutic settings. Developing microbiome-targeted therapeutics is hampered by the intricacy of microbiome-host interactions, study population diversity, and the shortcomings of standardized microbiome analysis methods [5].

9.1. Heterogeneity in Gut Microbiome Composition

Significant inter-individual diversity in the gut microbiome can be attributed to factors such as geography, drug usage, nutrition, lifestyle, and genetics. These variations make it challenging to identify universal microbial signatures linked to cardiovascular risk and to create therapies that target the microbiome in a way that works for everyone [3, 6].

9.2. Limitations in Microbiome Research Methodologies

The metagenomics, metabolomics, and 16S rRNA sequencing methods used in current microbiome research are limited in their ability to capture functional microbial interactions. Furthermore, reproducibility and comparability between studies are impacted by variations in sample collection, sequencing depth, and bioinformatics methodologies [3,9].

9.3. Challenges in Clinical Translation of Microbiome-Based Therapies

Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are examples of microbiome-targeted therapies that encounter difficulties in clinical translation, despite encouraging preclinical results. Before microbiome-based

treatments can be extensively used, issues like host immune responses, individual microbial diversity, and long-term safety concerns need to be resolved [5,6].

9.4. Need for Large-Scale, Longitudinal Studies

The cross-sectional nature of many current microbiome studies makes it difficult to prove a link between the development of cardiovascular disease and gut flora. To learn more about how gut microbiota evolves over time and reacts to nutritional or pharmaceutical interventions, large-scale, longitudinal research including a variety of populations are required [3,6].

9.5. Ethnic and Regional Variability in Microbiome-CVD Interactions

Cardiovascular risk is influenced by regional and ethnic variations in microbiome makeup, hereditary factors, and dietary practices. Personalized microbiome-based treatments require research on ethnically diverse populations, especially in underrepresented areas [5,6].

10. Results

According to research, changes in the gut microbiota cause systemic inflammation, metabolite synthesis, and immunological regulation, all of which accelerate the development of CVD. While SCFAs have protective effects on endothelial function and blood pressure management, TMAO levels are associated with increased cardiovascular risk. Increased LPS levels, hepatic lipid buildup, and vascular inflammation are linked to gut dysbiosis, which supports the idea that microbial metabolism plays a part in the pathophysiology of CVD. Probiotics and dietary changes are two examples of clinical therapies that have demonstrated promise in lowering inflammation, improving lipid profiles, and lowering cardiovascular risk factors. Individual responses to microbiome-based treatments are impacted by ethnic and genetic variations in gut microbiota composition, underscoring the necessity of tailored strategies.

11. Discussion

A new focus for the prevention and treatment of cardiovascular disease is the gut-heart axis. Interventions that support SCFA-producing bacteria and enhance gut barrier integrity may help lessen the impact of dysbiosis-driven inflammation and microbial metabolites like TMAO and PAG, which increase the risk of CVD. Precision medicine techniques are required since the effectiveness of microbiome-based treatments is dependent on host metabolism, dietary practices, and individual microbial diversity. Clinical translation is still difficult despite encouraging results because of study variability, methodological constraints, and a lack of established standards. In order to improve microbiome-targeted therapies for cardiovascular health, future studies should concentrate on combining metagenomics, metabolomics, and host genetics.

12. Conclusion

A new area of cardiovascular research called the gut-heart axis emphasizes the vital role that gut bacteria plays in the pathophysiology of cardiovascular disease (CVD). Atherosclerosis, hypertension, heart failure, and myocardial infarction are all exacerbated by dysbiosis, which has also been connected to systemic inflammation, dysregulation of cholesterol metabolism, and the generation of microbial metabolites. Important metabolites that modulate vascular function, lipid metabolism, and immunological responses include bile acids, short-chain fatty acids (SCFAs), and trimethylamine N-oxide (TMAO). Although there is potential for reducing the risk of CVD using microbiome-targeted therapies such as dietary changes, probiotics, prebiotics, and enzyme inhibitors, there are still many obstacles to overcome in clinical application. The necessity for individualized treatment approaches is highlighted by the heterogeneity in gut microbiota composition, the absence of standardized microbiome analysis techniques, and the variation in individual reactions to microbiome-based medicines. Large-scale, longitudinal studies that use multi-omics approaches should be the focus of future research in order to create focused microbiome-based therapies for cardiovascular health. Gut microbiota manipulation may be a promising approach to CVD prevention and therapy as microbiome science and precision medicine advance, opening the door for microbiome-integrated cardiology in clinical settings.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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